INPLASY PROTOCOL

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Comparison of age on the efficacy and safety of immune checkpoint inhibitors in patients with non-small cell lung cancer: a systematic review and meta-analysis

Su, MQ[1]; Du, Y[2]; Wang, M[3]; Song, M[4]; Yu, LP[5].

Review question / Objective: **Wheare there is age-dependent influence in patients with advanced or metastatic non-small cell lung cancer treated on immune checkpoint inhibitors?**
Condition being studied: **Immunotherapy of non-small cell lung cancer has entered a new stage. More and more studies have confirmed the efficacy of immune checkpoint inhibitors on NSCL. We intend to study whether patients of different ages are suitable for different types of immune checkpoint inhibitors.**
Information sources: **We will search articles in three electronic database including Pubmed, EMBASE and Cochrane Lirary. All the English publications until 31 Dec 2019 will be searched without any restriction of countries or article type. The database search terms used were 'immunotherapy', 'immune checkpoint inhibitor', 'immunother*', 'PD-1', 'programmed cell death 1 receptor', 'PD-L1', 'Programmed Cell Death Ligand 1', 'CTLA-4', 'cytotoxic T-lymphocyte-associated protein 4', 'Ipilimumab', 'Tremelimumab', 'Cemiplimab', 'Atezolizumab', 'Avelumab', 'Toripalimab', 'Sintilimab', 'Camrelizumab', 'Nivolumab', 'Pembrolizumab', 'Durvalumab', and 'Carcinoma, Non-Small-Cell Lung', 'non small cell lung cancer'. The electronic database search will be supplemented by a manual search of the reference lists of included articles.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 April 2020 and was last updated on 21 April 2020 (registration number INPLASY202040130).

INTRODUCTION

Review question / Objective: **Wheare there is age-dependent influence in patients with advanced or metastatic non-small cell lung cancer treated on immune checkpoint inhibitors?**

Condition being studied: **Immunotherapy of non-small cell lung cancer has entered a new stage. More and more studies have confirmed the efficacy of immune checkpoint inhibitors on NSCL. We intend to study whether patients of different ages**

are suitable for different types of immune checkpoint inhibitors.

METHODS

Search strategy: We will search articles in three electronic database including Pubmed, EMBASE and Cochrane Lirary. All the English publications until 31 Dec 2019 will be searched without any restriction of countries or article type. The database search terms used were 'immunotherapy', 'immune checkpoint inhibitor', 'immunother*', 'PD-1', 'programmed cell death 1 receptor', 'PD-L1', 'Programmed Cell Death Ligand 1', 'CTLA-4', 'cytotoxic T-lymphocyte-associated protein 4', 'Ipilimumab', 'Tremelimumab', 'Cemiplimab', 'Atezolizumab', 'Avelumab', 'Toripalimab', 'Sintilimab', 'Camrelizumab', 'Nivolumab', 'Pembrolizumab', 'Durvalumab', and 'Carcinoma, Non-Small-Cell Lung', 'non small cell lung cancer'. The electronic database search will be supplemented by a manual search of the reference lists of included articles.

Participant or population: We will study patients with advanced or metastatic non-small cell lung cancer who have been enrolled in randomized trials of immunotherapy versus chemotherapy. We choose 65 years old as a cutoff age to investigate immune checkpoint inhibitors efficacy and safety in different patients population. The study must refer to patients' age, so we will exclude a study that cannot analysis by age.

Intervention: The intervention that we study is the use of immune checkpoint inhibitors, include anti-PD-1 antibodies(Pembrolizumab, nivolumab, cemiplimab, toripalimab, sintilimab, camrelizumab), anti-PD-L1 antibodies(atezolizumab, avelumab, durvalumab), anti-CTLA-4 antibodies(ipilimumab and tremelumimab).

Comparator: We will study the effects of these agents compared to chemotherapy, including platinum doublet chemotherapy, or docetaxel, gemcitabine, or vinorelbine monotherapy as a standard care agent. And we also include placebo-controlled studies.

Study designs to be included: This study will include any randomized controlled studies using the drugs in question in comparison to standard of care chemotherapy.

Eligibility criteria: RCTs meeting all of the following criterias will be included: (1) Randomized controlled studies in patients who were diagnosed with advanced or metastatic non-small cell lung cancer; (2) ICIs includes PD-1, PD-L1, CTLA-4 or their combination; (3) In intervention group, ICIs were administered alone or in combination with other drugs(chemotherapy or other immunological drugs); (4) Participants treated with control regimen without an ICIs; (4) Studies have datas available for HR and 95% credible interval (CI) of OS(overall suivival) or PFS (progression-free survival) or both of the two outcomes based on a cut-off age.

Information sources: We will search articles in three electronic database including Pubmed, EMBASE and Cochrane Lirary. All the English publications until 31 Dec 2019 will be searched without any restriction of countries or article type. The database search terms used were 'immunotherapy', 'immune checkpoint inhibitor', 'immunother*', 'PD-1', 'programmed cell death 1 receptor', 'PD-L1', 'Programmed Cell Death Ligand 1', 'CTLA-4', 'cytotoxic T-lymphocyte-associated protein 4', 'Ipilimumab', 'Tremelimumab', 'Cemiplimab', 'Atezolizumab', 'Avelumab', 'Toripalimab', 'Sintilimab', 'Camrelizumab', 'Nivolumab', 'Pembrolizumab', 'Durvalumab', and 'Carcinoma, Non-Small-Cell Lung', 'non small cell lung cancer'. The electronic database search will be supplemented by a manual search of the reference lists of included articles.

Main outcome(s): The main coutcome of this review is the difference of overall suivival(OS) and progression-free survival (PFS)in young and old patients with Non-small cell lung cancer who underwent immunotherapies.

Additional outcome(s): We will also study the toxicity of immune therapy specifically between older and younger patients.

Data management: Two authors will independently extract data. Any disagreement will be resolved by discussion until consensus is reached or by consulting a third author. The following data will be extracted: author, year of publication, country where the study was conducted, trial phase, line of treatment, study period, study population and baseline characteristics, details of the intervention and control conditions, outcomes from eligible trials.

Quality assessment / Risk of bias analysis: Two reviewers will independently assesses the quality of the selected studies according to The Cochrane Collaboration's Tool for randomized controlled trials. Items will be evaluated in three categories: Low risk of bias, unclear bias and high risk of bias. The following characteristics will be evaluated: Random sequence generation; allocation concealment; blinding of participants and personnel to the study protocol; incomplete outcome data; and selective reporting. Any disagreements were resolved by discussion and consensus.

Strategy of data synthesis: We will extract HRs for death and their 95% CIs from eligible studies that examined immunotherapy efficacy in younger and older patients. The HR and CI values will combined using the random effects model. We will evaluate the heterogeneity of the summary HRs using the I2 statistic, which yields the percentage of variability in the effect estimate due to heterogeneity rather than sampling error. Publication bias will be assessed by a funnel plot for meta-analysis and quantified by the Egger method. All p values are two-sided.

Subgroup analysis: We will consider subgroups such as class of immune checkpoint inhibitor, type of immune checkpoint inhibitor, histotype, line of treatment, mask of the studies.

Sensibility analysis: We evaluated the heterogeneity of the summary HRs using the I2 statistic, which yields the percentage of variability in the effect estimate due to heterogeneity rather than sampling error. Publication bias was assessed using funnel plots and Egger's test. All reported p values are two sided.

Language: English.

Country(ies) involved: China.

Keywords: Carcinoma, Non-small cell lung; PD-1; PD-L1; CTLA-4; Aged.